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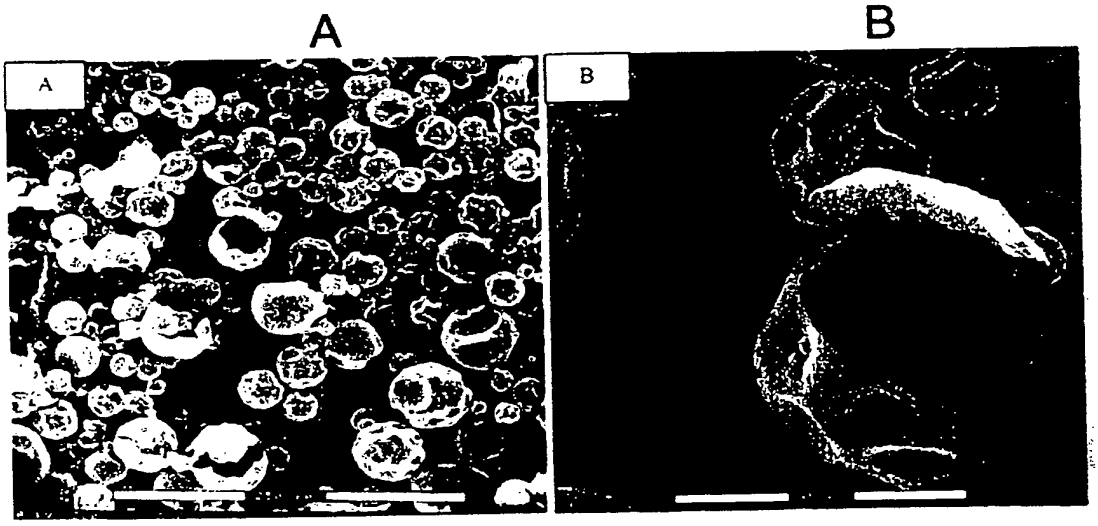
(54) Title: PHOTOSTIMULATED PHASE SEPARATION ENCAPSULATION



(57) Abstract: The invention provides a method of preparing microcapsules which comprises dissolving or dispersing a radiation-sensitive polymer in a first liquid, dispersing the first liquid in a continuous phase of a second liquid that is more polar than the first liquid, and irradiating the polymer to increase its polarity and form a membrane, and also the membranes prepared.

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PHOTOSTIMULATED PHASE SEPARATION ENCAPSULATION

The present invention relates to microcapsules, to methods of making them, and to their use.

Background of the Invention

Microcapsules and matrices containing an encapsulated active ingredient are known for many purposes. In some instances, slow release of the encapsulated ingredient is required. Materials that have been encapsulated in microcapsules and hydrogel matrices include pharmaceuticals, pesticides, fungicides, herbicides, bactericides, dyes, inks, chemical reagents and flavouring materials, and semiochemicals, that is materials that will modify the behaviour of animal species, for example pheromones.

In the area of crop protection, insect pheromones are proving to be a biorational alternative to conventional hard pesticides. In particular, attractant pheromones can be used effectively in controlling insect populations by disrupting the mating process. Here, small amounts of species-specific pheromone are dispersed over the area of interest during the mating season, raising the background level of pheromone to the point where the male insect cannot identify and follow the plume of attractant pheromone released by his female mate.

Mechanical dispensers, hollow fibres, impregnated plastic twist-ties, and polymer microcapsules are some of the delivery devices used to deliver the pheromone throughout the mating period of the insect, typically two to six weeks.

Polymer microcapsules in particular promise to serve as efficient delivery vehicles, as they: a) are easily prepared by a number of interfacial and precipitation polymerizations, b) enhance the resistance of the pheromone to oxidation and irradiation during storage and release, c) may in principle be tailored to control the rate of release of the pheromone fill,

and (d) permit easy application of pheromones by, for example, spraying using conventional spraying equipment.

One known method of forming pheromone-filled microcapsules involves dissolving pheromone and a diisocyanate in xylene and dispersing this solution into an aqueous solution followed by addition of a diamine. A polyurea membrane forms rapidly at the interface between the continuous aqueous phase and the dispersed xylene droplets, resulting in formation of microcapsules containing the pheromone and xylene; see for example PCT international application WO 98/45036, Li, Nielson, Sengupta, published 15 October 1998. Although this method is useful and yields valuable products it does have some limitations. For instance, isocyanates are highly reactive compounds and it is difficult to encapsulate compounds that react with the isocyanate. Hence, it is difficult to encapsulate compounds containing hydroxyl groups such as alcohols.

The present invention provides an encapsulation method that does not require use of an isocyanate reactant. Furthermore, the present invention provides a method to photochemically control microcapsule formation.

Summary of the Invention

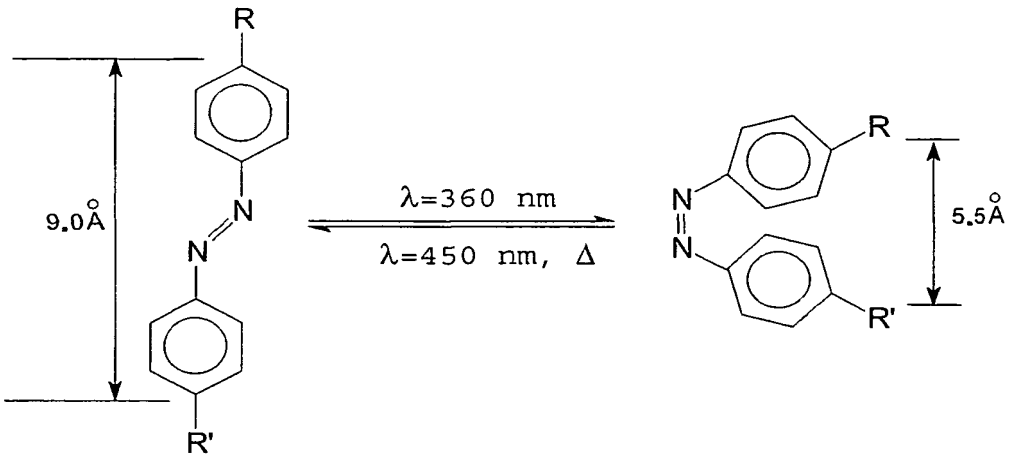
In one aspect, the present invention provides a method of preparing microcapsules which comprises dissolving or dispersing a radiation-sensitive polymer in a first liquid, dispersing the first liquid in a continuous phase of a second liquid that is more polar than the first liquid, and irradiating the polymer to increase its polarity, thereby causing it to migrate from the first liquid to the interface between the first and second liquids and form a membrane.

In another aspect, the invention extends to the microcapsules prepared. It is also possible to encapsulate

additional material that is soluble in the first liquid, for instance, pheromones that are released slowly over time. The invention also extends to microcapsules encapsulating such materials.

Description of Preferred Embodiments

In some embodiments use is made of a photoinduced trans-cis isomerization of an azobenzene. This causes change in the geometry and the dipole moment, as shown in the following equation:

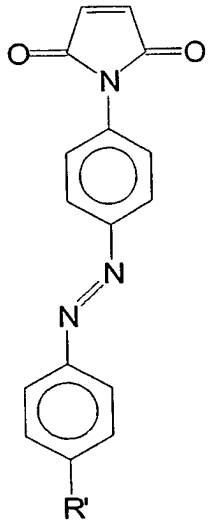


As shown, UV light of 360 nm wavelength causes azobenzenes to isomerize from the trans to the cis configuration. Azobenzenes are much more polar in the cis configuration than in the trans configuration. Hence, if azobenzenes in the more stable trans configuration are present in an oil droplet dispersed in a continuous phase in an oil-in-water emulsion, irradiation with light of 360 nm will cause the azobenzenes to isomerize to the more polar cis configuration. If the azobenzenes are present as part of a membrane-forming polymer then the polymer will migrate from the oil phase to the aqueous phase, if the solubility parameters of the organic phase are suitable, i.e. if the organic phase is a near theta solvent for the polymer, and the polymer will form a membrane at the oil/water interface.

Although the cis-trans isomerization of individual azobenzene molecules is reversible, as shown by the equation above, it is found that the formation of membranes by irradiation is not reversible.

Membrane-forming polymers in which azobenzene moieties can be incorporated include polymers that contain anhydride moieties, for example, styrene-maleic anhydride (SMA) copolymers. Such copolymers, containing 50% or more of styrene, are readily available, or readily made, and it is possible to modify a preformed SMA copolymer to incorporate azobenzene moities or to copolymerise an azobenzene-containing monomer with styrene and maleic anhydride or maleimide, or both maleic anhydride and maleimide.

It is possible to form an SMA-azobenzene copolymer by copolymerization of styrene, maleic anhydride and an azobenzene-containing monomer, for example a 4-phenylazomaleinanil, of formula:



wherein R' is hydrogen, alkyl, alkoxy, alkoxyalkyl, amino, monoalkylamino or dialkylamino, the alkyl moieties containing up to 18, preferably up to 6, carbon atoms.

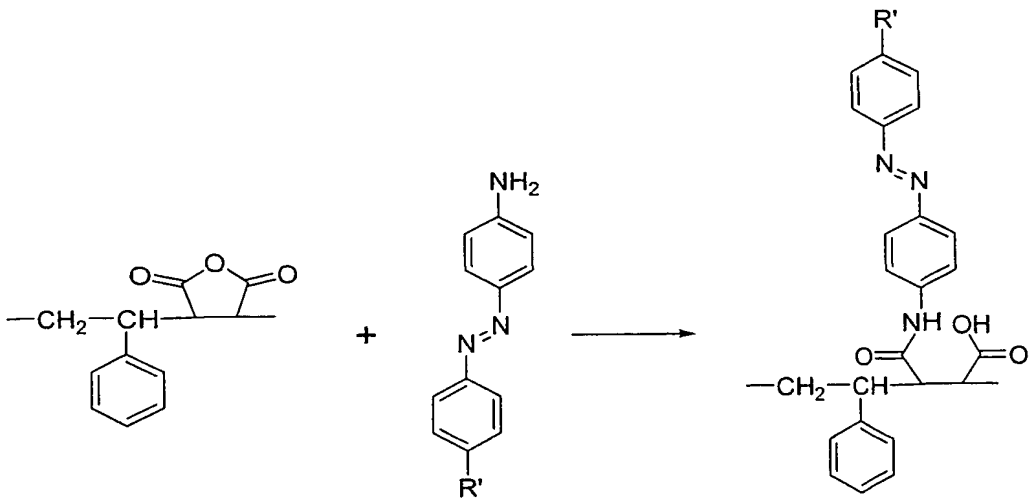
Although styrene and maleic anhydride are preferred co-monomers for use with the azobenzene-containing moiety, it is possible to use other unsaturated polymerisable monomers in addition to, or instead of these. For instance it is possible to use styrene, α-methylstyrene, or styrene or α-methylstyrene that is substituted in the benzene ring of the styrene moiety. As substituent, mention is made of lower alkyl groups having up to 18 carbon atoms, preferably up to 6 carbon atoms. The extra alkyl substituents on, for example, p-methylstyrene and p-tert.-butylstyrene render the copolymer less polar and more soluble in the water-immiscible solvents such as xylene and toluene that are preferred for use in interfacial reactions. Other possible unsaturated copolymerisable monomers that may be present, in place of or in addition to styrene, include olefins such as ethylene, conjugated dienes such as 1,3-butadiene and isoprene, alkyl acrylates and methacrylates, especially lower alkyl such as the methyl, ethyl and, preferably, the butyl and ethylhexyl esters, vinyl acetate, acrylonitrile, methacrylonitrile, acrylamides, methacrylamides and unsaturated ethers such as alkyl vinyl ethers, for instance, the methyl and ethyl ethers. Also mentioned are the vinyl sulphoxides and vinyl sulphones. By use of these various monomers and also by selection of the amount of maleic anhydride in the polymer it is possible to vary the polarity and hence the solubility of the polymers. This is of value as it is desirable that the polymer shall be of only limited solubility in the first liquid.

The azobenzene moiety can be introduced into a polymer in other ways. For instance, an azobenzene compound bearing a reactive group can undergo a condensation reaction with pendant reactive groups of a polymer. For example, an azobenzene bearing a primary or secondary amino group can react with a glycidyl group pendant from a polymer chain. A glycidyl group can be provided by polymerizing glycidyl acrylate or

methacrylate, or copolymerizing these with other unsaturated copolymerizable monomers. Suitable unsaturated copolymerisable monomers include those mentioned above in the discussion of anhydride-containing copolymers.

Similarly, polymers with acid chloride groups can condense with an azobenzene-containing compound that also bears a primary or secondary amino group or a hydroxy group

A preformed SMA copolymer can be reacted with an aminoazobenzene. Attack of the aminoazobenzene on the anhydride moieties results in the formation of one carboxyl moiety and one amide moiety bearing the azobenzene, in accordance with the following equation:



The amino azobenzene can bear substituents, preferably in the 4'-position, i.e., R' in the formula of the aminoazobenzene can be, for example hydrogen, an alkyl group, an alkoxy group, an ether group, an amino group or a monoalkylamino or dialkylamino group, the alkyl moieties of

these groups containing up to 18, preferably up to 6 carbon atoms.

The reaction can be carried out at reflux temperature in a polar solvent, for example tetrahydrofuran (THF). The functionalized polymer can be recovered by cooling in admixture with a non-polar solvent, for example heptane, to cause it to precipitate.

In a similar reaction, SMA can be reacted with a hydroxy-azobenzene compound, resulting in the opening of an anhydride moiety and the formation of a carboxyl moiety and an ester moiety bearing the azobenzene.

Styrene-maleic anhydride copolymers containing 50 mol% or more of styrene are readily available commercially, or are readily prepared. Any of these can be used, although it is preferred that the copolymer contains at least about 5 mol%, more preferably at least about 14 mol% of maleic anhydride. The number of anhydride moieties present in the copolymer, and the number of those maleic anhydrides that are reacted with an azobenzene-containing compound will determine the frequency of the occurrence of radiation-sensitive groups along the polymer chain. This clearly can be controlled by the choice of the molar ratio of maleic anhydride moieties to azobenzene-containing compound. Preferably this ratio may be in the range from 1:1 to 20:1, more preferably in the range from 1:1 to 5:1.

In the above description, maleic anhydride moieties have been used in the incorporation of the photoreactive azobenzene moiety in a polymer. Other unsaturated polymerisable monomers that contain anhydride moieties can be used in addition to, or instead of, maleic anhydride for this purpose. Examples of these other anhydride moieties include itaconic anhydride, citraconic(methylmaleic) anhydride,

ethylmaleic anhydride, 1,2-cyclohexene-1,2-dicarboxylic acid anhydride and 1,2-cyclohexene-4,5-dicarboxylic acid anhydride.

It is possible to use functional groups present in the polymer to enhance the strength of the membrane formed by the irradiation. For instance, an SMA copolymer reacted with stoichiometric amounts of 4-aminoazobenzene will contain free carboxyl groups. After the irradiation, these carboxyl groups can be coupled with, for instance, polyamines or polyols, especially in the presence of suitable water-soluble coupling reagents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC). Further, a polymer containing substoichiometric amounts of aminoazobenzene will contain unreacted anhydride moieties. These anhydride moieties would be particularly susceptible to reaction with polyamines or polyols added to the aqueous phase after the irradiation.

Suitable water-soluble primary and secondary polyamines preferably primary diamines include those of formula (I):

$$H_2N(CH_2)_n NH_2 \qquad (I)$$

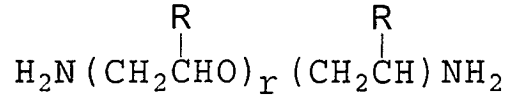
wherein n is an integer from 2 to 10, preferably 2 to 6. Mention is made of hexamethylenediamine. Also suitable are mixed primary/secondary amines and mixed primary/secondary/tertiary amines. Mixed primary/secondary amines include those of formula (II):

$$H_2N(CH_2\underset{\displaystyle R}{\underset{|}{C}}HNH)_m CH_2\underset{\displaystyle R}{\underset{|}{C}}HNH_2 \qquad (II)$$

wherein m is an integer from 1 to 1,000, preferably 1 to 10, and R is hydrogen or a methyl or ethyl group. Mention is made of tetraethylenepentamine (TEPA). Suitable primary/secondary/tertiary amines include compounds like those

of formula (II) but modified in that one or more of the hydrogen atoms attached to a non-terminal nitrogen atom of the compound of formula (II) is replaced by a lower aminoalkyl group such as an aminoethyl group. The commercial product of tetraethylenepentamine usually contains some isomers branched at non-terminal nitrogen atoms, so that the molecule contains one or more tertiary amino groups. All these polyamines are readily soluble in water, which is suitably used as the second continuous phase. Other suitable polyamine reactants include polyvinylamine, polyethyleneimine, and polyallylamine. Primary and secondary amino groups will react with anhydride moieties. Tertiary amino groups will catalyse the reaction of the primary and secondary amino groups.

Also suitable are polyetheramines of general formula (III):



$$H_2N(CH_2\underset{\displaystyle R}{\underset{|}{C}}HO)_r(CH_2\underset{\displaystyle R}{\underset{|}{C}}H)NH_2 \qquad \text{(III)}$$

where r is an integer from 1 to 20, preferably 2 to 15, more preferably 2 to 10, and R is hydrogen, methyl or ethyl. Such compounds are available under the trademark Jeffamine from Huntsman.

If an amine is to be used in a post irradiation reaction, the amine must contain at least two amino groups capable of reacting with the anhydride, i.e., primary or secondary amino groups. Hence, the compound must be, at least, a diamine, but it may contain more than two amino groups; see for example compounds of formula (II). In this specification the term "diamine" is used to indicate a compound that has at least two reactive amino groups but the term does not necessarily exclude reactants that contain more than two amino groups. Similar remarks apply to the term "diol".

Reactants that can be used in post-irradiation reaction also include compounds that contain both amino and

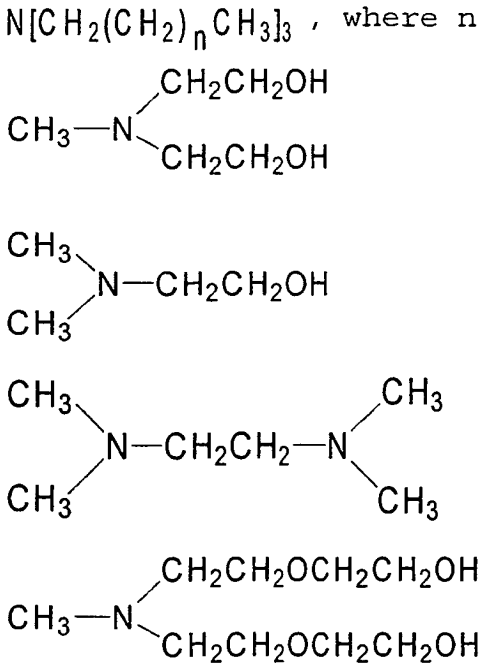
hydroxyl groups. As examples of such compounds there are mentioned monoethanolamine, diethanolamine, triethanolamine, dialkylethanolamines, N-alkyl-diethanolamines and N,N-dimethyl-2-amino(ethoxy)ethanol.

The reaction between, for example, maleic anhydride and polyamine, results in the opening of the anhydride ring with the formation of one amide moiety and one ammonium salt moiety between a carboxyl group and an amine. Hence, the membrane formed is, in part, ionic. It is possible to subject this product to elevated temperature to dehydrate it to form a maleimide.

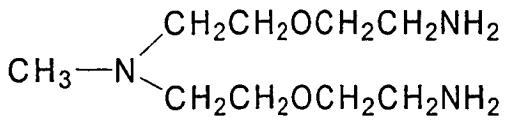
If a material is to be encapsulated in the microcapsules formed, that material is dissolved or dispersed in the first liquid, together with the radiation-sensitive polymer. This material must not be so reactive with the polymer that it interferes with the radiation-induced reaction of the polymer. Alcohols can be encapsulated. The ability to encapsulate alcohols is of particular significance. The pheromone of the codling moth is E,E-8,10-C_{12} alcohol and it has been difficult to encapsulate this pheromone by the previously known technique involving isocyanate. The present invention permits encapsulation of alcoholic compounds, including alcoholic pheromones and should permit encapsulation of codling moth pheromone.

A catalyst can be incorporated with the amine in the aqueous phase to speed post-irradiation reactions with polyamines or polyols. Suitable catalysts include tertiary amines. The tertiary amine, in the amount used, should be freely soluble in the water present in the reaction mixture. The simplest tertiary amine is trimethylamine and this compound, and its C_2, C_3 and C_4 homologues can be used. It is of course possible to use tertiary amines containing a mixture of alkyl groups, for instance methyldiethylamine. The tertiary

amine can contain more than one tertiary amine moiety. It may also contain other functional groups provided that those other functional groups do not interfere with the required reaction, or the functional groups participate beneficially in the required reaction. As an example of a functional group that does not interfere there is mentioned an ether group. As examples of groups that participate there are mentioned primary and secondary amine groups, and hydroxyl groups. Examples of suitable tertiary amines include compounds of the following structures:



and



Of the tertiary amines triethylamine (TEA) is preferred.

The amount of the tertiary amine required is not very great. It is conveniently added in the form of a solution containing 0.5g of TEA per 10mL of water. Usually 0.5% by

weight of this solution, based on the total weight, suffices, although 0.7% by weight may be required in some cases. The amount used does not usually exceed 1%, although no disadvantage arises if more than 1% is used.

Catalysts other than tertiary amines can be used. Metal salts that are soluble in an organic solvent used as the first liquid can be used. Mention is made of titanium tetraalkoxides available under the trademark Tyzor from DuPont, and stannous octanoate, although these should not be used when there is also present in the organic solvent an alcohol to be encapsulated.

In other embodiments of the invention it is possible to use a polyol in a post-irradiation reaction. Suitable polyols include diols of formula (IV):

$$HO(CH_2)_n OH \quad (IV)$$

wherein n is an integer from 2 to 10, preferably 2 to 4, and of formula (V):

$$HO(CH_2\underset{\displaystyle R}{\underset{|}{C}}HO)_m CH_2\underset{\displaystyle R}{\underset{|}{C}}HOH \quad (V)$$

wherein m is an integer from 1 to 10 and R is hydrogen or a methyl or ethyl group. A catalyst can be used and suitable catalysts include the tertiary amines and other catalysts mentioned above.

The first liquid, that serves as the dispersed phase, is a liquid in which the radiation-sensitive polymer can be dispersed or dissolved and in which any material to be encapsulated can be dispersed or dissolved. It should be immiscible, or at least only partially miscible, with the second liquid. While the limits on what is meant by "partially miscible" are not precise, in general a substance is considered to be water-immiscible if its solubility in water is less than

about 0.5% by weight. It is considered to be water-soluble if its solubility is greater than 98%, i.e., if 1 gram of the substance is put in 100 grams of water, 0.98 gram would dissolve. A substance whose solubility falls between these approximate limits is considered to be partially water-miscible. Desirably, the first liquid is a marginal solvent for the polymer reactant, and has a boiling point in the vicinity of 100°C. The properties of the first liquid, which will become encapsulated with the active material that is to be released, will affect the rate of release of that active material. Selection of a first liquid has to be made with these considerations in mind. Suitable candidates for use as the first liquid include alkylbenzenes such as toluene and xylene, ethers such as methyl tert.-butyl ether, ketones such as methylisobutylketone, esters such as ethyl acetate and propyl acetate, halogenated aliphatic hydrocarbons such as dichloromethane, and aliphatic nitriles such as butyronitrile. Mixtures of solvents can be used. There can also be used co-solvents to change the properties of solvents or solvent mixtures. As co-solvents there are mentioned aliphatic liquids such as kerosene and also cyclic hydrocarbons such as cyclohexane. For instance, styrene-maleic anhydride copolymer containing 14% maleic anhydride is soluble in all of these solvents, whereas copolymer containing 50% maleic anhydride is soluble only in ethylacetate, dichloromethane and butyronitrile.

The second liquid that forms the continuous phase is preferably water or an aqueous solution with water as the major component, or another polar solvent.

It is desirable that the first liquid shall be a near theta solvent for the particular polymer, that it shall be immiscible with the second liquid, or at least not completely miscible with the second liquid, shall have a relatively high

boiling point, preferably above 100°C, and shall permit the radiation-sensitive polymer to precipitate on irradiation. The names and properties of some of the candidates used as the first liquid, whose solubility parameters are close to the solubility parameters of the copolymers, are given in Table 1.

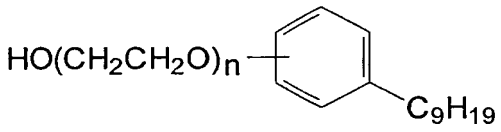
Table 1

Solvent	Solubility parameter $(cal/cm)^{1/2}$	Dielectric constant	Miscibility with water	Boiling Point
Ethylacetate	9.1	6.0814(293.2 K)	Partially Miscible	76-77
Methyliso-butylketone	8.4	13.11(293.2 K)	Immiscible	117-118
Xylenes	8.8	2.2735(293.2 K)	Immiscible	137-144
Toluene	8.9	2.379(296.35 K)	Immiscible	110
Dioxane	7.9	2.2189(293.2 K)	Miscible	100-102
THF	9.1	7.52(295.2 K)	Miscible	65-67

Cont. of Table 1

Butyroni-trile	10.5	24.83(293.2 K)	Partially Miscible	115-117
Ethylene glycol dimethyl ether	8.6	7.30(296.7)	Miscible	85
Dichloro-methane	9.3	8.93(298.0 K)	Partially Miscible	40
Methyl ethyl Ketone	9.3	18.56(293.2 K)	Miscible	80
Propyl Acetate			Immiscible	102

Surfactants and emulsifiers can be used to assist in dispersion of the first liquid, i.e. the oil phase, in the second liquid. Mention is made of poly(vinylalcohol), polyvinylpyrrolidones and nonylphenyl-oligo-ethylene glycol, available under the trademark IGEPAL. These are of formula:



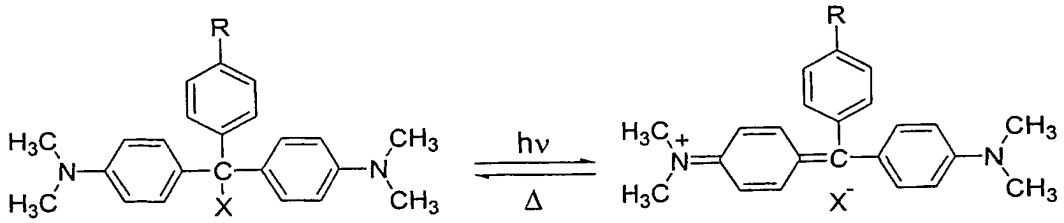
where n has an average value from about 9 to about 13. IGEPAL 630, indicating a molecular weight of about 630, is mentioned. IGEPAL 630 is preferred to poly(vinylalcohol) as it results in smaller microcapsules. Other suitable surfactants and emulsifiers include polyethyleneglycol alkyl ethers, for example, $C_{18}H_{35}(OCH_2CH_2)_nOH$, where n has an approximate value of about 20, available under the trade-mark BRIJ 98.

Ionic surfactants can be used. Sodium dodecyl sulphate (SDS) is mentioned as an example of an anionic surfactant.

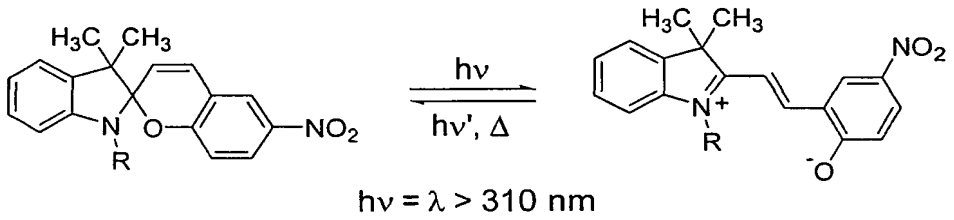
The first liquid can be dispersed in the second liquid by dropping the first liquid into a stirred bath of the second liquid. The first liquid then forms droplets throughout the continuous phase of the second liquid. The reaction mixture is then irradiated to change the polarity of the polymer and cause capsule formation. Any second reactant for post-irradiation reaction to enhance the membrane formation may be present in the second liquid before the first liquid is added. In an alternative embodiment, the second reactant is not present in the second liquid when the first liquid has been dispersed, but is added subsequently, after irradiation.

The membrane forming raction can be carried out at any temperature between about 0°C and about 70°C, preferably between about 10°C and about 40°C. Most preferably the reaction is carried out at about room temperature, i.e. about 20 to about 25°C. The lamp used to irradiate may also give off heat, so it may be desirable to apply cooling.

It is possible to use compounds other than azobenzenes to render polymers radiation-sensitive, so that their polarity can be changed by irradiation. Examples of such compounds include triphenylmethane/leucoderivatives such as the following:



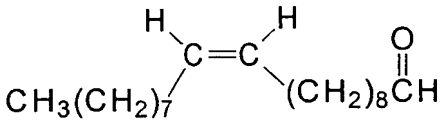
where R is CH=CH2 and X is OH. Such compounds are described in Advances in Polymer Science, Volume 94, Masatrilo Ilie "Photoresponsive Polymers", the disclosure of which is incorporated herein by reference. Other compounds that can be used include spirobenzopyrans, for example



$h\nu = \lambda > 310$ nm

where R is an alkyl group, for instance a methyl or ethyl group.

As examples of materials to be encapsulated, particular mention is made of insect pheromones. In the notation used below to describe the structure of the pheromones, the type (E or Z) and position of the double bond or bonds are given first, the number of carbon atoms in the chain is given next and the nature of the end group is given last. To illustrate, the pheromone Z-10 C19 aldehyde has the structure:



Pheromones may in fact be mixtures of compounds with one component of the mixture predominating, or at least being a significant component. Mentioned as examples of significant or predominant components of insect pheromones, with the target species in brackets, are the following: E/Z-11 C14 aldehyde (Eastern Spruce Budworm), Z-10 C19 aldehyde (Yellow Headed Spruce Sawfly), Z-11 C14 acetate (Oblique Banded Leafroller), Z-8 C12 acetate (Oriental Fruit moth) and E,E-8,10 C12 alcohol (Codling moth).

An example of a ketone that is a pheromone is E or Z 7-tetradecen-2-one, which is effective with the oriental beetle. An ether that is not a pheromone but is of value is 4-allylanisole, which can be used to render pine trees unattractive to the Southern pine beetle.

In one preferred embodiment, the product of the microencapsulation process is a plurality of microcapsules having a size in the range of from about 1 μm to about 5000 μm, preferably 20 μm to 2000 μm. Particularly preferred microcapsules have sizes in the range from about 10 μm to about 60 μm, more preferably about 20 to about 30 μm, and an encapsulated pheromone contained within the membrane. The microcapsules can be used in suspension in water to give a suspension suitable for aerial spraying. The suspension may contain a suspending agent, for instance a gum suspending agent such as guar gum, rhamsan gum or xanthan gum.

Incorporation of a light stabilizer, if needed to protect encapsulated material, is within the scope of the invention. Suitable light stabilizers include the tertiary phenylene diamine compounds disclosed in Canadian Patent No. 1,179,682, the disclosure of which is incorporated by reference. The light stabilizer can be incorporated by dissolving it, with the pheromone, in the oil phase. Antioxidants and UV absorbers can also be incorporated. Many hindered phenols are known for this purpose. Mention is made of antioxidants available from Ciba-Geigy under the trade-marks Irganox 1010 and 1076. As UV absorbers there are mentioned Tinuvin 292, 400, 123 and 323 available from Ciba-Geigy.

To assist in determining the distribution of sprayed microcapsules it is possible to include a coloured dye or pigment in the microcapsules. The dye should be oil-soluble and can be incorporated, with the pheromone, in the oil phase.

It will be used only in a small amount and will not significantly affect the membrane-forming reaction. Alternatively, or additionally, an oil-soluble or oil-dispersible dye can be included in the aqueous suspension of microcapsules, where it is absorbed by the microcapsule shell. Suitable oil-soluble or oil-dispersible dyes can be obtained from DayGlo Color Corporation, Cleveland, Ohio, and include Blaze Orange, Saturn Yellow, Aurora Pink, and the like.

Although the invention has been described largely with reference to encapsulation of pheromones, other molecules that are active in nature can be encapsulated in a similar manner. As examples there are mentioned linalool, terpineol, fenchone, and keto-decenoic acids and hydroxy-decenoic acids, which encourage activity of worker bees. Encapsulated 4-allylanisole can be used to make pine trees unattractive to the Southern pine beetle. Encapsulated 7,8-epoxy-2-methyloctadecane can be used to combat the nun moth or the gypsy moth. All these applications, and microcapsules containing these materials, are within the scope of the present invention.

Other compounds of interest for encapsulation and controlled release include mercaptans. Some animals mark territory by means of urine, to discourage other animals from entering that territory. Examples of such animals include preying animals such as wolves, lions, dogs, etc. Ingredients in the urine of such animals include mercaptans. By dispersing microcapsules containing the appropriate mercaptans it is possible to define a territory and discourage particular animals from entering that territory. For example, the urine of a wolf includes a mercaptan, and distribution of microcapsules from which this mercaptan is gradually released to define a territory will discourage deer from entering that territory. Other materials that can be encapsulated and used

to discourage approach of animals include essences of garlic, putrescent eggs and capsaicin.

Other compounds that can be included in the microcapsules of the invention include perfumes, pharmaceuticals, fragrances, flavouring agents and the like.

It is also possible to encapsulate materials for uses other than in nature. Mention is made of dyes, inks, adhesives and reactive materials that must be contained until they are to be used, for instance, by controlled release from a microcapsule or by rupture of a microcapsule.

Other materials that can be encapsulated are mentioned in PCT international application WO 98/45036 mentioned above, the disclosure of which is incorporated herein by reference.

It is found that some of the microcapsules of this invention are pH-sensitive. The microcapsules shrink in acid and swell in base. Release of encapsulated material is slowed when the microcapsules are shrunken and is accelerated when the microcapsules are swollen. As styrene-maleic anhydride-azobenzene copolymers are biocompatible, microcapsules of the invention can be used to supply pH-sensitive pharmaceutical materials to the intestine. In the acidic stomach environment the microcapsules are shrunken and little or no release of active ingredient occurs. On entering the intestine, with its alkaline environment, the microcapsules swell and release of encapsulated active ingredient occurs.

The invention is further illustrated with reference to the accompanying drawings and the following non-limiting examples.

Figures 1A and 1B are environmental scanning electron microscope (ESEM) images of microcapsules prepared in Example 5;

Figures 2A and 2B are ESEM images of microcapsules prepared in Example 6;

Figures 3A and 3B are optical photomicrographs of capsules formed in Example 7.

Experimental

Materials:

Poly(styrene-maleic anhydride) of 50% maleic anhydride content was obtained from Aldrich, and was also prepared according to the procedure described below. Poly(styrene-maleic anhydride), with 32% and 14% maleic anhydride content, 4-aminoazobenzene, maleic anhydride, 4-phenylazomaleinanil (PAMA), N-phenylmaleimide (PMA) and methylethylketone were obtained from Aldrich and used as received. Styrene was purchased from Aldrich, and passed neat through a short alumina column to remove inhibitors.

Example 1

Typical preparation of poly(styrene-maleic anhydride) of 50% maleic anhydride:

Equimolar amounts of styrene (0.052 mole, 5.3g) and maleic anhydride (0.052 mole, 5.0g) were dissolved in 75mL methylethylketone in a 250 mL round bottom flask fitted with a magnetic stirrer and a reflux condenser. Nitrogen was bubbled through the reaction flask. Azobisisobutyronitrile (AIBN) ($6.09\ 10^{-2}$ mmole, 0.01g) was added to the flask, and the polymerization allowed to proceed at 70°C for 24 hours. After cooling, the reaction mixture was precipitated into an excess of heptane (700mL), and the resulting copolymer dried under

vacuum at room temperature overnight. The yield of copolymer was 7.2g, 70%, M_w=45,000,MWD=1.53.

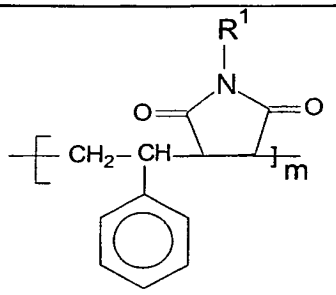
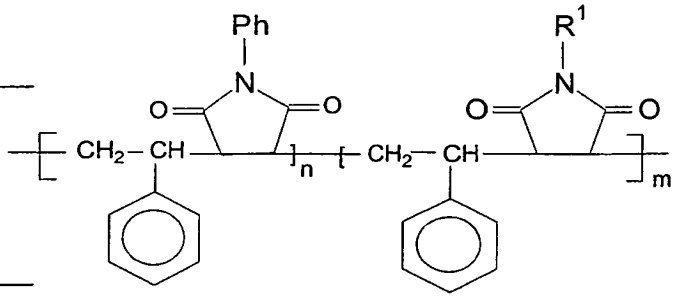
Example 2

Typical preparation of styrene-maleimide copolymers

Preparation of poly(styrene(50%)-phenylmaleimide(20%)-4-phenylazomaleinanil(30%))(S-PAMA30-PMA20)copolymer: 0.66 g(3.84 mmol) of N-phenylmaleimide, 1.6 g (5.76 mmol) of 4-phenylazomaleinanil (PAMA) and 1g (9.6 mmol) of styrene were dissolved in 20 mL dioxane in a 100 mL round flask. AIBN (0.02 g, 0.12 mmol) was added to the flask, and the polymerization allowed to proceed at 70°C for 24 hours under nitrogen. After cooling, the reaction mixture was precipitated into an excess of methanol (500mL), and the resulting copolymer dried under vacuum at room temperature overnight. The yield of copolymer was 2.53g, 78%, M_w-32,000,MWD=1.72.

Table 2 shows styrene-maleimide based azobenzene functionalized copolymer.

Table 2

Copolymer (Abbreviations)	Structure (R^1=azobenzene)
Poly(styrene(50)-4-phenylazomaleinanil(50)) S-PAMA50	
Poly(styrene(50)-(4-phenylazomaleinanil (10)/phenylmaleimide(40)) S-PAMA10-PMA40	
Poly(styrene(50)-(4-phenylazomaleinanil (20)/phenylmaleimide(30)) S-PAMA20-PMA30	
Poly(styrene(50)-(4-phenylazomaleinanil (30)/phenylmaleimide(20)) S-PAMA30-PMA20	
Poly(styrene(50)-(4-phenylazomaleinanil (40)/phenylmaleimide(10)) S-PAMA40-PMA10	

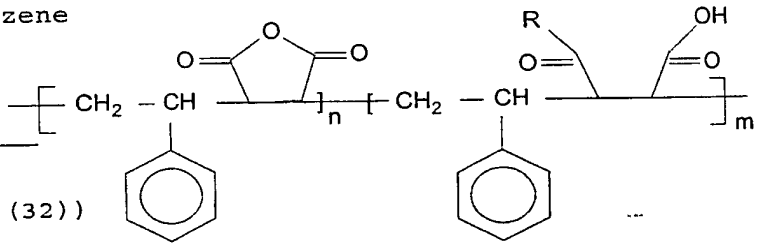
Example 3

Typical functionalization reaction

Poly(styrene-(50%)-maleic anhydride (50%)), molecular weight 45,000 from Example 1) (5g, 28 mmole anhydride) was refluxed with 4-aminoazobenzene (5.0 g, 25 mmol) in 100 mL THF overnight. The reaction mixture was cooled, and precipitated into an excess of heptane to isolate the yellow functionalized polymer.

Table 3 shows styrene-maleic anhydride based azobenzene-functionalized copolymers.

Table 3

Copolymer (Abbreviations)	**Structure** (R=aminoazobenzene)
Poly(styrene(50)-maleic anhydride(50)) functionalized with aminoazobenzene SMA50-AAB	
Poly(styrene(68)-maleic anhydride (32)) functionalized with aminoazobenzene SMA32-AAB	
Poly(styrene(86)-maleic anhydride (14)) funtionalized with aminoazobenzene SMA14-AAB	

Equipment and Characterization

A UV reactor consisting of a set of 8 Rayonet photochemical reactor lamps RPR-3500A lining the inner wall of a vertical aluminum cylinder of 12 cm diameter, cooled with a small fan, was used for the irradiations.

A Philips-2020 Environmental Scanning Electron Microscope (ESEM) was used to obtain electron microscope images. Dilute dispersions of microcapsules were deposited on aluminum stubs, dried at room temperature and sputter-coated with a 5 nm gold layer. Optical microscopy was performed using a Olympus BH-2 microscope, equipped with a Kodak DC 120 Digital Camera.

General Procedure for Irradiation

During the photo-induced encapsulations, the oil phase, consisting of a solution of one of the azobenzene functionalized polymers in a suitable solvent or solvent mixture, was dispersed in an aqueous phase containing an emulsifier. The resulting emulsion was irradiated at 350 nm at room temperature for about an hour, after which time the emulsion droplets had turned into liquid-filled polymer microcapsules. The polymer phase separated from the solvent during irradiation, and migrated to the organic/water interface to form the capsule wall.

Example 4

Styrene-maleimide base copolymers

Poly(styrene-(50%)-4-phenylazomaleinanil (50%))(S-PAMA50)

Homogeneous solutions of S-PAMA50 copolymers in methylisobutylketone showed phase separation upon irradiation at 350 nm for 30-90 minutes. The yellow solutions of the azobenzene functional polymers became almost clear following

the irradiation, with the polymers precipitating into an orange solid. In a solvent with a higher dielectric constant, such as THF, no solubility change was observed upon irradiation.

Example 5

Typical Method for the Photochemical Preparation of S-PAMA50 Microcapsules

The following methods described the preparation of microcapsules prepared from S-PAMA50, mol. wt. 15,000 in methyl isobutyl ketone. 100 mL deionized water containing 1g polyvinylalcohol (80% hydrolyzed, 9000 - 10000 Da) was placed into a 200 mL beaker, stirred at 450 rpm, and the oil phase consisting of 0.5g S-PAMA50 dissolved in 10 mL methylisobutylketone was added dropwise over 60 seconds to form an oil-in-water emulsion. After an additional 20 min of stirring, the emulsion was transferred to a UV-reactor and irradiated for 1 hr. A glass cold finger was submerged into the emulsion to keep its temperature near room temperature. Following irradiation, the resulting aqueous dispersion of microcapsules was stored at room temperature.

Figures 1A and 1B show environmental scanning electron microscope (ESEM) images of microcapsules prepared by irradiating aqueous emulsions of methylisobutylketone containing 5% by weight of S-PAMA50.

Clearly the polymer capsule walls are thin, in the order of 500nm. The enlarged area shown in Figure 1B illustrates how some of the capsules have burst during ESEM processing.

Example 6

Effect of polymer concentration in the oil phase

The analogous encapsulation, as used in Example 5 with an emulsion of methylisobutylketone containing 10% by weight instead of 5% of the same S-PAMA50, leads to much thicker capsule shells (Figures 2A and 2B). Figure 2A shows a representative section of the electron micrograph image of the capsules obtained after 45 minutes irradiation. Figure 2B shows capsule wall fragments obtained by manually crushing some of the capsules. The thick wall of these capsules prepared from a 10% by weight solution of S-PAMA50 in methylisobutylketone is remarkable and may indicate porosity.

The concentration of copolymer in the organic phase is reflected in the shell thickness of the microcapsules. Lowering the polymer content of the oil phase produces thinner shells, as seen from electron micrographs of the fractured microcapsules prepared from emulsions with 5% of copolymer and 10% of copolymer (Figures 1B and 2B).

Lower polymer concentration narrows the microcapsule size distribution, and decreases the average size of the capsules. A higher concentration of the polymer in the droplet phase leads to the formation of correspondingly larger droplets because more viscous liquids are less easily broken up to smaller droplets.

Example 7

Styrene-maleimide based copolymers with less than 50% of azo groups

Styrene-maleimide based copolymers with less than 50% of UV-sensitive groups (Table 2B) were also prepared. It was found that S-PAMA10-PMA40 copolymer, which has only 10% of UV-sensitive groups precipitates out upon UV-irradiation from the mixture THF/heptane (3/1) and also from ethylene glycol dimethyl ether. This result indicates that 10% of photosensitive groups on the polymer is enough to cause the

solubility change of the polymeric solution upon irradiation. It was also found that only S-PAMA50 is soluble in the non-polar solvents such as methylisobutylketone and toluene. To dissolve copolymers containing less PAMA in non-polar solvents (toluene, xylene, methylisobutylketone) an addition of solvent with high solubility parameter such as dichloromethane or an addition of a polar, and optionally proton-donating solvent such as aniline was required (Table 4). Alternatively, copolymers incorporating tert.-butyl styrene or other less polar monomers would be useful in conjunction with the non-polar solvents mentioned above. A correlation can be made between the solubility of the copolymers in non-polar solvents and the amount of PAMA copolymer incorporated in the copolymer. The copolymers with high content of PAMA (near 50%) are more hydrophobic than the copolymers with low content of PAMA. It is indicated that PAMA is a more hydrophobic monomer than PMA.

Table 4

Solubility of 0.5% polymeric solution of styrene-maleimide based copolymers in non-polar solvents

Copolymer	**Xylene**	**Toluene**	**Methyl isobutyl-ketone**	**Toluene/ aniline**	**Toluene/ CH_2Cl_2**
S-PAMA50	i	s	s	s	S
S-PAMA40-PMA10	i	i	i	s(no data)	s(~9/1)
S-PAMA30-PMA20	i	i	i	s(~8/1)	s(~6/1)

Cont. of Table 4

S-PAMA20-PMA30	I	i	i	s(~2/1)	s(~3/1)
S-PAMA10-PMA40	I	i	i	s(~1/1)	s(~1/1)

s=soluble, i=insoluble

Capsules were prepared from S-PAMA30-PMA20, mol. wt. 32,000 dissolved in toluene/aniline (8/1)and toluene/dichloromethane (6/1) mixtures according to the general procedure (Fig. 3A and 3B).

The capsules were prepared at room temperature, stirring speed 450 rpm with sodium dodecyl sulphate (0.3%) as surfactant. The aqueous phase was 100 mL in volume and in each case the oil phase consisted of 0.3 g of polymer in 7 mL of total organic phase. Capsules in Figure 3A were made using a toluene/aniline (8/1) mixture as first liquid (core oil) and capsules in Figure 3B used a toluene/dichloromethane (6/1) mixture.

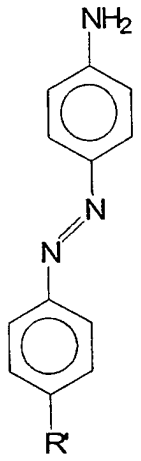
CLAIMS:

1. A method of preparing microcapsules which comprises dissolving or dispersing a radiation-sensitive polymer in a first liquid, dispersing the first liquid in a continuous phase of a second liquid that is more polar than the first liquid, and irradiating the polymer to increase its polarity and form a membrane.

2. A method according to claim 1, wherein the radiation-sensitive polymer contains azobenzene moieties.

3. A method according to claim 2, wherein the azobenzene moieties are introduced into a styrene-maleic anhydride polymer by reacting the polymer with an aminoazobenzene.

4. A method according to claim 3, wherein the aminoazobenzene is of formula

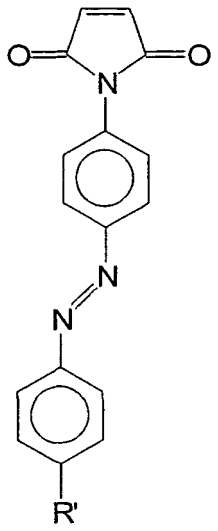


where R' is hydrogen, an alkyl group, an alkoxy, an ether group, an amino group or a monoalkylamino or dialkylanino group, the alkyl moieties of these groups containing up to 18 carbon atoms.

5. A method according to claim 2, wherein the azobenzene moieties are introduced into the polymer by copolymerization of styrene, maleic anhydride and a 4-phenylazomaleinanil.

6. A method according to claim 2, wherein the azobenzene moieties are introduced into the polymer by copolymerization of styrene and a 4-phenylmaleinanil.

7. A method according to claim 6, wherein the 4-phenylmaleicnanil is a compound of formula



where R' is hydrogen, alkyl, alkoxy, alkoxyalkyl amino, monoalkylamino or dialkylamino group, the alkyl moieties of these groups containing up to 18 carbon atoms.

8. A method according to any one of claims 1 to 7, wherein the radiation-sensitive irradiated polymer contains anhydride moieties and, after irradiation, a polyamine or polyol is reacted with the anhydride moieties to crosslink and to strengthen the membrane.

9. A method according to claim 2, wherein the azobenzene moieties are incorporated into a polymer by a condensation reaction between an azobenzene-containing compound and a corresponding pendant reactant group of a polymer chain.

10. A method according to claim 9, wherein the pendant reactant group is a glycidyl moiety or an acid chloride group.

11. A method according to any one of claims 1 to 10, wherein a material for controlled release is dissolved or dispersed in the first liquid and becomes encapsulated in the microcapsules.

12. A method according to claim 11, wherein the material for controlled release is a semiochemical.

13. A method according to claim 12, wherein the semiochemical is a pheromone.

14. Microcapsules whose membrane is formed by irradiation of a radiation-sensitive polymer.

15. Microcapsules according to claim 14, wherein the radiation-sensitive polymer comprises azobenzene moieties.

16. Microcapsules according to claim 14 or 15 encapsulating a material that will undergo controlled release.

17. Microcapsules according to claim 16, wherein the material that will undergo controlled release is a semiochemical.

18. Microcapsules according to claim 17, wherein the semiochemical is a pheromone.

19. A method of controlling insect population by applying to the habitat of the insects microcapsules according to claim 17 or 18.

FIG. 1A

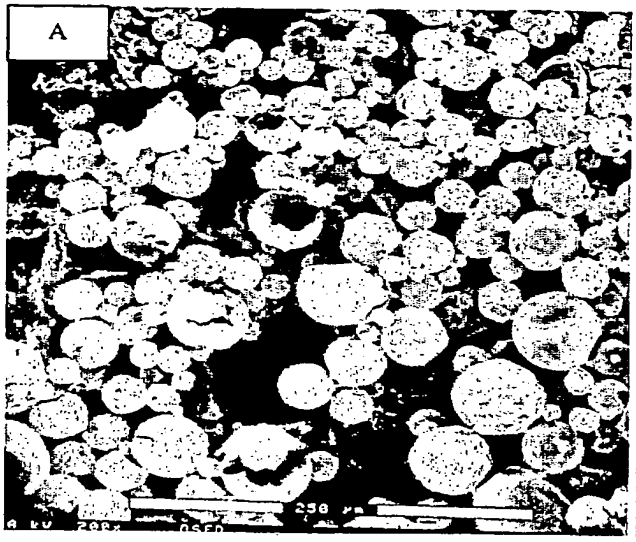


FIG. 1B

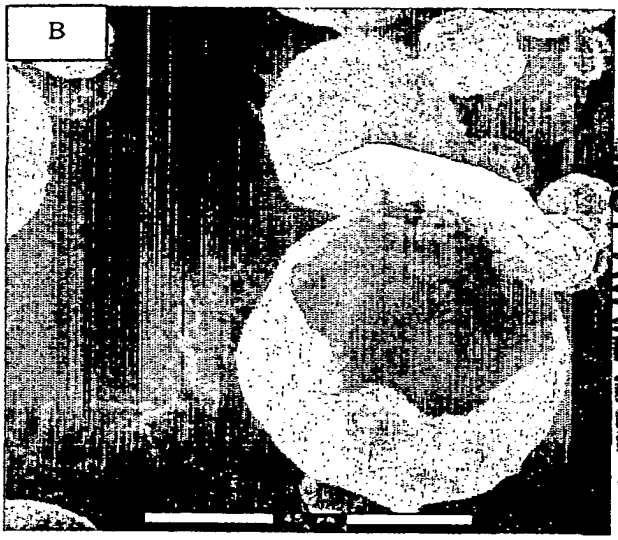


FIG. 2A

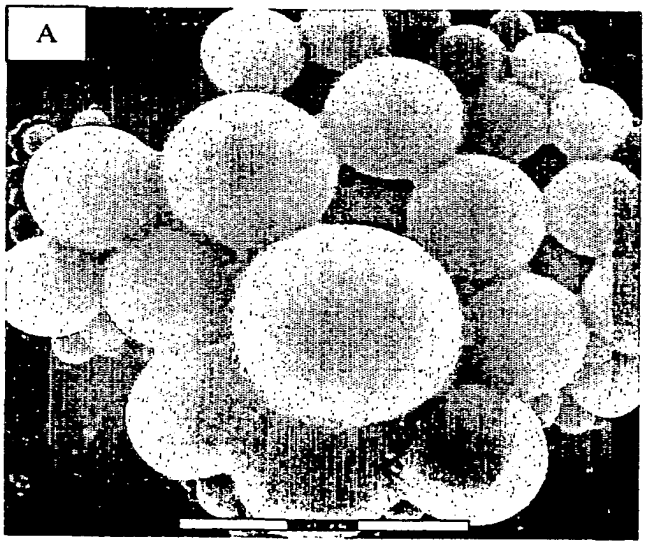


FIG. 2B

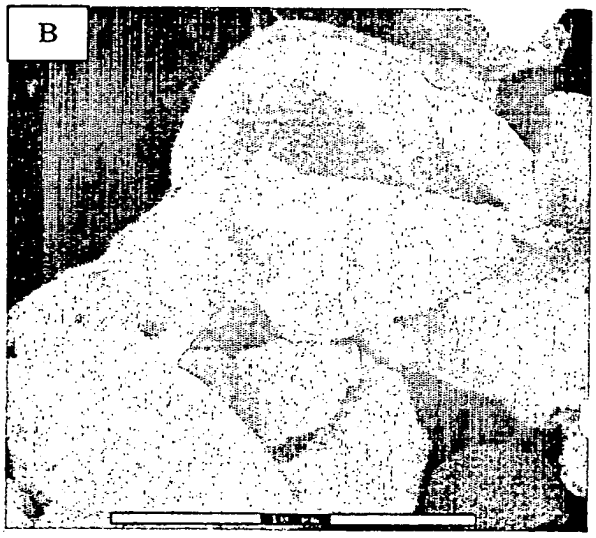


FIG.3A

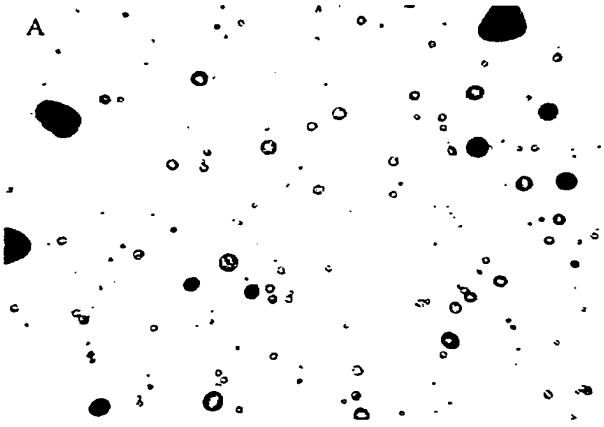


FIG. 3B

INTERNATIONAL SEARCH REPORT

In ... al Application No
PCT/CA 01/00869

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J13/10 A01N25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 013, no. 063 (C-568), 13 February 1989 (1989-02-13) -& JP 63 256129 A (YOSHIHARU TSUJITA;OTHERS: 01), 24 October 1988 (1988-10-24) abstract; figure 8 ---	1-19
A	PATENT ABSTRACTS OF JAPAN vol. 003, no. 142 (C-065), 24 November 1979 (1979-11-24) & JP 54 119373 A (AGENCY OF IND SCIENCE & TECHNOL), 17 September 1979 (1979-09-17) abstract ---	1-19
A	US 3 405 071 A (ZOILA REYES) 8 October 1968 (1968-10-08) the whole document -----	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2001	12/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Willsher, C

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]nal Application No
PCT/CA 01/00869

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